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THE HIDDEN BURDEN OF DIABETIC NEPHROPATHY: EVIDENCE FROM AN AUTOPSY-BASED ANALYSIS

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ABSTRACT

Aim To analyse the number of patients with Diabetic Nephropathy at autopsy and classify cases of Diabetic Nephropathy based on histological findings.

Materials and Methods: A total number of 2524 autopsy cases (age >12 years) were screened from the period of January 2016 to June 2021 of which 144 cases showing findings of DM Nephropathy were included in the study. Medicolegal and paediatric autopsy cases were excluded from the study. Gross features of various organs were recorded. sections from kidneys were studied using Haematoxylin and eosin stain and other special stains wherever required. Diabetic nephropathy classification was done according to Histopathologic classification for DN which was established in 2010.

Results and Discussion: Out of total 144 cases of Diabetic Nephropathy, 61 (42.36%) cases belonged to class II, 74 (51.39%) cases belonged to class III and 9 (6.25%) cases belonged to class IV. Clinical history of Diabetic nephropathy was present in 113 (78.47%) cases while 31 (21.53%) cases showed features of Diabetic Nephropathy as an incidental finding at autopsy. Average age of these 144 patients was 56 years (range 22- 86 years). 86 were males, 58 were females with male to female ratio of 1.5:1.

Conclusion: 144 cases of diabetic nephropathy included 61 cases (42.36%) of class II DN, 74 cases (51.39%) of class III DN and 9 cases (6.25%) of class IV DN. 31 cases (21.53%) showed features of diabetic nephropathy as an incidental finding at autopsy which were otherwise not diagnosed clinically during patients' life. Autopsy provides a vital doorway to study, identify and detect clinically missed cases of diabetic nephropathy providing more accurate statistical data that can help to recognize the real burden of many such diseases which might get missed otherwise without help of autopsy.

KEYWORDS: Diabetic Nephropathy, Autopsy, Diabetes Mellitus

INTRODUCTION

The prevalence of diabetes mellitus (DM) is around 425 million people worldwide, and this figure is predicted to increase to over 600 million by 2045.[1]

Diabetes Mellitus (DM) is classified as type 1 DM and type 2 DM. Type 1 DM includes those cases that are primarily due to destruction of pancreatic β- cells. Type 2 DM is most prevalent form of the disease which results from insulin resistance with an insulin secretory defect. Diabetic nephropathy is a clinical syndrome seen in a patient with diabetes mellitus that is characterized by persistent albuminuria, worsening proteinuria, declining Glomerular Filtration Rate (GFR), increased blood pressure, and progressive renal failure.[2,3,4]

Diabetic nephropathy is a common cause of end stage renal disease worldwide.(3) Approximately a third of patients with type 1 insulin- dependent diabetes mellitus (IDDM) and type 2 non-insulin-dependent diabetes mellitus (NIDDM) develop diabetic nephropathy.(2) Two thirds of patients with diabetic nephropathy develop renal failure requiring either dialysis or renal transplantation.(5) Such patients frequently develop other complications such as cardiovascular diseases including hypertension and stroke, resulting in increased risk of early mortality.[3,4]

A relatively high proportion of diabetic nephropathy which was clinically underdiagnosed yet histologically proven suggesting that diabetic nephropathy may develop even before onset of clinical findings.[6]

Prevention of DN is the key to avoiding disease progression, and most therapeutic measures have focused particularly on patients with incipient nephropathy (microalbuminuria) or eGFR decrease. Recent KDIGO guideline recommendations on diabetes management are centered on T2DM patients with

CKD (urine albumin to creatinine ratio >30 mg/g or eGFR <60 mL/min/73 m2), yet DN prevention measures should be established in earlier stages before microalbuminuria develops.[1]

Renal biopsy in T2DM patients is usually indicated in those with significant renal manifestations such as severe proteinuria, microscopic hematuria, rapid unexplained worsening of kidney function, or over 30% decline in eGFR after initiating RAAS inhibition. In this regard, some studies have analyzed early DN lesions in patients without clinical signs of this involvement (microalbuminuria). Nonetheless, although not a routine technique, renal biopsy remains the gold standard of DN diagnosis and recent evidence supports determining renal histologic involvement in this disease. For this reason, very few studies to date have analyzed renal histologic alterations in the early stages of T2DM.[1]

AIM

The main aim was to analyze the number of patients with Diabetic Nephropathy at autopsy and classify cases of Diabetic Nephropathy based on histological findings.

MATERIAL AND METHOD

Permission from Ethics Committee for Academic Research Projects (ECARP) was taken. Waiver of consent was taken from the ECARP.

A total number of 2524 autopsy cases (age >12 years) were screened from the period of January 2016 to June 2021. Out 2524 autopsy cases 144 cases showing findings of DM Nephropathy were included in the study. Medicolegal and paediatric autopsy cases were excluded from the study.

Organs were preserved in 10% formalin for adequate duration. During the study period, Gross features of various organs were recorded. For our study, sections from kidneys were studied using Haematoxylin and eosin stain and other special stains such as Periodic acid Schiff, Congo red and Elastic Van Gieson wherever required.

Clinical details were retrieved by going through indoor papers as per availability.

This retrospective and prospective study included autopsy cases (age >12 years) with histological findings of diabetic nephropathy with or without history of diabetic nephropathy was carried out at Department of Pathology in a tertiary care hospital, western India from January 2016 to June 2021.

Histological findings data was collected & inserted in excel sheet. Diabetic nephropathy classification was done according to Histopathologic classification for DN which was established in 2010.

Classification of diabetic nephropathy was done as follows:
Histopathologic classification for DN was established in 2010. This may be applied to diabetic nephropathy in both types 1 and 2 DM. This classification uses only glomerular lesions in order to make it easy to use and reproducible.

Class I: mild or nonspecific changes with GBM thickening proven by electron microscopy.

Class II: mesangial expansion defined as greater than the width of two mesangial nuclei in two lobules in greater than 25% of glomeruli. This class is further subdivided into mild (less than the diameter of a capillary lumen) and severe (greater than the diameter of a capillary lumen).

Class III: presence of at least one Kimmelstiel-Wilson nodule and less than 50% globally sclerotic glomeruli.

Class IV: global sclerosis in greater than 50% of glomeruli in combination with lesions from the other three classes.[2,6,7]

For statistical analysis, appropriate statistical tests were applied wherever applicable.

RESULTS

A total of 2524 adult autopsies (>12 years age) were studied out during the period, out of which 144 cases of diabetic nephropathy are included in this study. Age of patients ranged from 22 to 86 years and mean age 56 years (Chart no. 1). 86 patients were male and 58 were females with male female ratio of 1.5:1. Gross morphological features of kidneys for Diabetic Nephropathy were similar in type 1 as well as type 2 Diabetes Mellitus. The kidney size appeared increased, decreased and normal in 67, 28, 49 cases respectively. Weight of kidneys ranged from 45 grams to 380 grams with mean weight being 144 grams. Histological findings of diabetic nephropathy were seen in all of the major structural compartments of kidney i.e., glomeruli, extraglomerular vessels, interstitium and tubules.

Out of total 144 cases of Diabetic Nephropathy, 61 (42.36%) cases belonged to class II, 74 (51.39%) cases belonged to class III and 9 (6.25%) cases belonged to class IV. Class I diabetic nephropathy cases could not be identified due to unavailability of electron microscope.

Out of total 144 cases of Diabetic Nephropathy, clinical history of Diabetic nephropathy was present in 113 (78.47%) cases. These patients were receiving antidiabetic treatment in form of oral hypoglycaemic drugs and/or insulin from 3 years to 25 years duration while 31 (21.53%) cases showed features of Diabetic Nephropathy as an incidental finding at autopsy.

DISCUSSION

In this present study, out of these 144 cases of Diabetic Nephropathy, 61 (42.36%) cases belonged to class II identified by presence of mesangial expansion defined as greater than the width of two mesangial nuclei in two lobules in greater than 25% of glomeruli, 74 (51.39%) cases belonged to class III characterized by presence of at least one Kimmelstiel-Wilson nodule and less than 50% globally sclerotic glomeruli. 9 (6.25%) cases belonged to class IV characterized by global sclerosis in greater than 50% of glomeruli in combination with lesions showing other features of diabetic nephropathy.

Average age of these 144 patients was 56 years (range 22- 86

years). 86 were males, 58 were females with male to female ratio of 1.5:1. Clinical history of diabetic nephropathy was present in 113 (78.47%) cases while 31 (21.53%) cases showed features of diabetic nephropathy (positive PAS and negative Congo Red) as an incidental finding at autopsy and subsequent histopathology.

Klessens CQF et al[6] in a cohort autopsy study of 168 clinically diagnosed diabetic patients reported diabetic nephropathy in 106 cases (63%). These 106 cases of DN were classified as twenty-two cases (20.75%) of DN class I, thirty-three cases (31.13%) of DN class II, forty-five cases (42.45%) of DN class III and six cases (5.66%) of DN class IV. Average age of these 168 cases was 69 years. Diabetic nephropathy was detected at autopsy in 20 out of 106 (19%) cases. Interestingly, we found similar results and histomorphology features in our present study.

Perrone ME et al[8] in their study identified 22 cases (16%) of diabetic nephropathy however they classified diabetic nephropathy as mild to moderate (11 cases) and severe (11 cases) diabetic nephropathy based on glomerular findings.

D'Marco et al[1] showed that 4.8% cases were of class I, 42.9% cases were of class II, 9.5 % cases were of class III & 42.9% cases were of class IV type DM nephropathy. Our study showed similarity in terms of class II cases (42.36%). In contrast to D'Marco et al study our study showed higher percentage of class III cases (51.36%) & lower percentage of class IV cases (6.25%).

CONCLUSION

144 cases of diabetic nephropathy included 61 cases (42.36%) of class II DN, 74 cases (51.39%) of class III DN and 9 cases (6.25%) of class IV DN.

31 cases (21.53%) showed features of diabetic nephropathy as an incidental finding at autopsy which were otherwise not diagnosed clinically during patients' life. This suggests that there might be large number of undiagnosed hence untreated cases of DM nephropathy in community which needs attention of clinicians to provide better healthcare to patients.

Autopsy provides a vital doorway to study, identify and detect clinically missed cases of diabetic nephropathy. Furthermore, it provides more accurate statistical data that can help to recognize the real burden of many such diseases which might get missed otherwise without help of autopsy. Autopsy helps to discover large number of preventable renal lesions and autopsy kidneys do carry tremendous significance in proper diagnosis ultimately enlightening a scope to provide a better patient care.

LIMITATIONS OF STUDY

Unavailability of electron microscope for detection of class I diabetic nephropathy cases. Hence there might be a greater number of undiagnosed DM nephropathy cases, which may have been missed due to unavailability electron microscope.

CONFLICT OF INTEREST- None

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CHART NO. 1
DISTRIBUTION OF CASES ACCORDING TO AGE

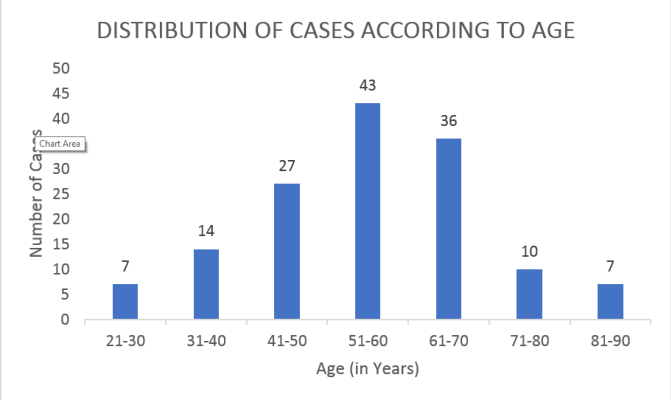

Chart no. 1 shows distribution of cases of Diabetic Nephropathy at autopsy.

TABLE NO. 1
CLASSIFICATION AND PRESENTATION OF CASES OF DIABETIC NEPHROPATHY AT AUTOPSY

	History of Diabetic Nephropathy Present	History of Diabetic Nephropathy Absent	Total No. of Cases
Diabetic Nephropathy Class I	--	--	--
Diabetic Nephropathy Class II	57	4	61
Diabetic Nephropathy Class III	50	24	74
Diabetic Nephropathy Class IV	6	3	9
Total No. Of Cases	113	31	144

Table no. 1 shows classification and presentation of cases of Diabetic Nephropathy at autopsy.

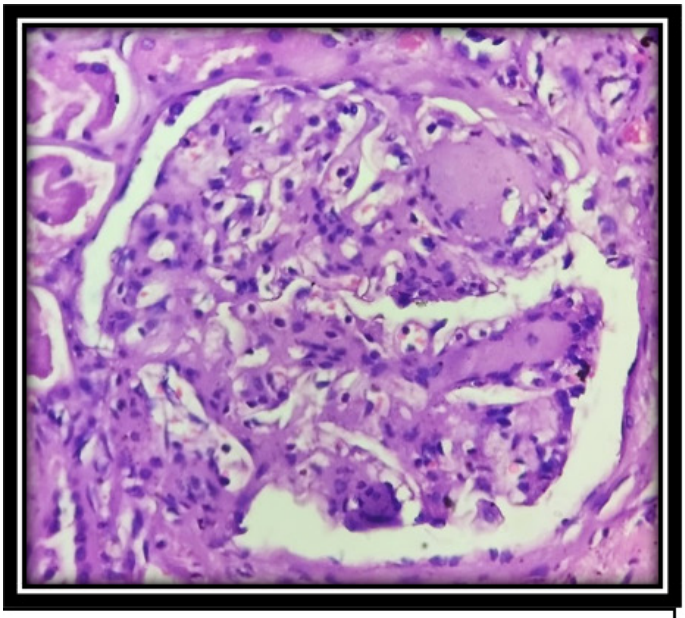

Fig 1-A) DIABETIC NEPHROPATHY (H & E, 400X)- glomeruli showing thickened glomerular basement membrane, nodular glomerulosclerosis.

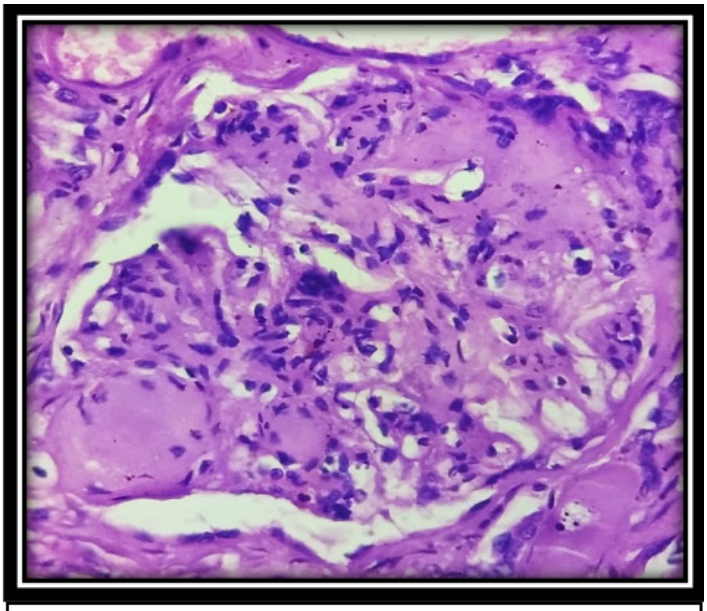

Fig 1-B) DIABETIC NEPHROPATHY (H & E, 400X)- glomeruli showing mesangial expansion and nodular glomerulosclerosis.

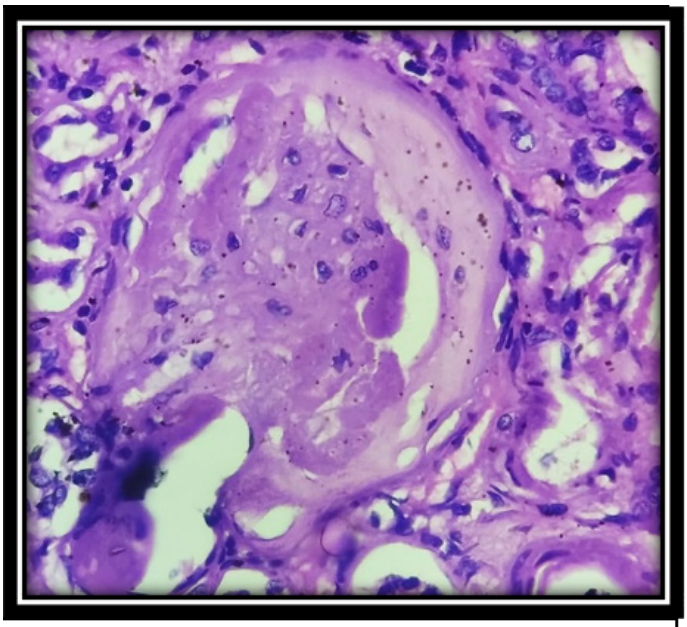

Fig 1-C) DIABETIC NEPHROPATHY (H & E, 400X)- glomeruli showing mesangial expansion and nodular glomerulosclerosis and capsular drop.

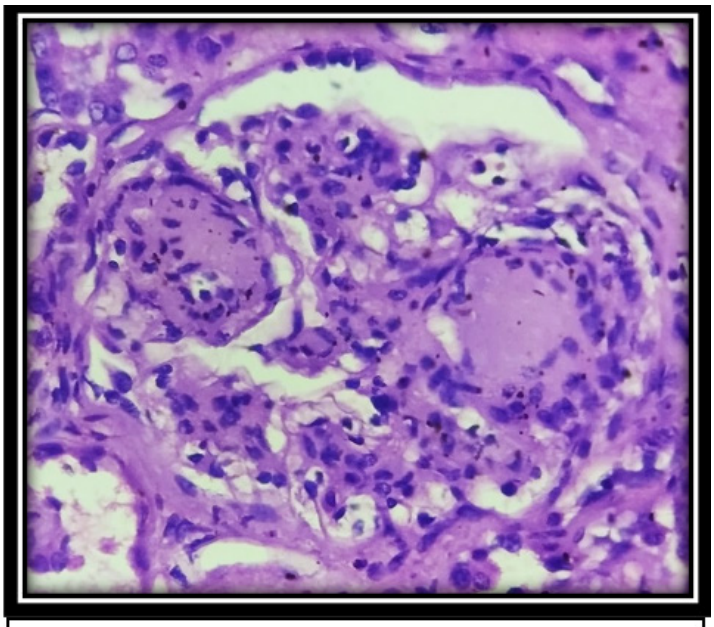

Fig 1-D) DIABETIC NEPHROPATHY (H & E, 400X)- glomeruli showing thickened glomerular basement membrane, nodular glomerulosclerosis.

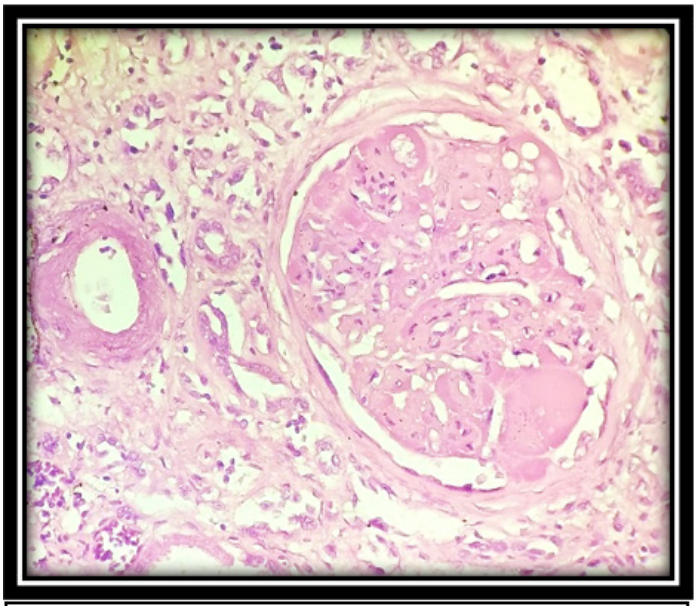

Fig 1-E) DIABETIC NEPHROPATHY (H & E, 100X)- microphotograph showing hyaline arteriolosclerosis and glomeruli showing nodular glomerulosclerosis and fibrin cap.

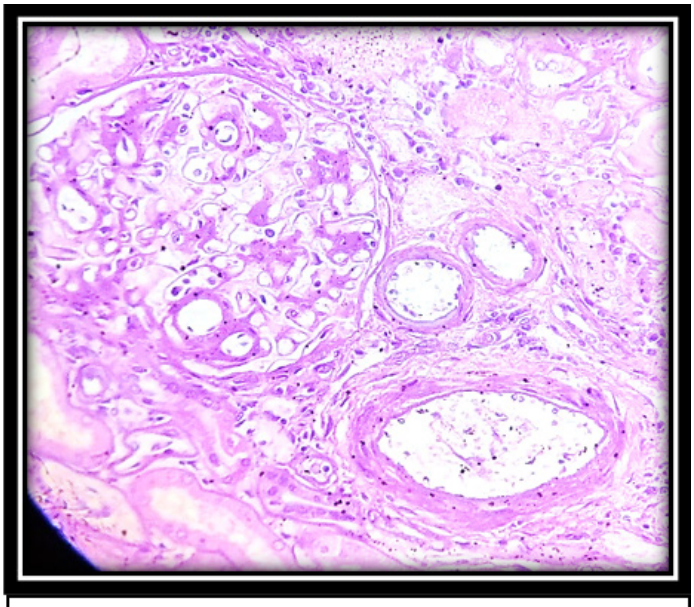

Fig 1-F) DIABETIC NEPHROPATHY (H & E, 100X)- hyaline hyaline arteriolosclerosis and glomeruli showing thickened glomerular basement membrane and mesangial expansion.

Legends of Images

Fig 1-A) DIABETIC NEPHROPATHY (H & E, 400X)- glomeruli showing thickened glomerular basement membrane, nodular glomerulosclerosis.

Fig 1-B) DIABETIC NEPHROPATHY (H & E, 400X)- glomeruli showing mesangial expansion and nodular glomerulosclerosis.

Fig 1-C) DIABETIC NEPHROPATHY (H & E, 400X)- glomeruli showing mesangial expansion and nodular glomerulosclerosis and capsular drop.

Fig 1-D) DIABETIC NEPHROPATHY (H & E, 400X)- glomeruli showing thickened glomerular basement membrane, nodular glomerulosclerosis.

Fig 1-E) DIABETIC NEPHROPATHY (H & E, 100X)- microphotograph showing hyaline arteriolosclerosis and glomeruli showing nodular glomerulosclerosis and fibrin cap.

Fig 1-F) DIABETIC NEPHROPATHY (H & E, 100X)- hyaline hyaline arteriolosclerosis and glomeruli showing thickened glomerular basement membrane and mesangial expansion.